Attorney Docket No. 1907.03 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Inventors: WETTSTEIN, *et al.*

Application No.: 09/972,035

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For: Tsg101-GAGp6 INTERACTION AND USE THEREOF

Group Art Unit: 1648

Examiner: Myron G. Hill

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7-28-2006

Date

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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Sir:

Applicants submit this Appeal Brief, in accordance with 37 C.F.R. § 41.37, five months from the filing of the Notice of Appeal, dated February 28, 2006. A petition for a three-month extension of time for filing this Appeal Brief is being concurrently filed herewith, and provisions for the payment of the three-month extension fee are provided therein. The Director is hereby authorized to charge the required Appeal Brief filing fee of $250.00, for a small entity, as set forth in 37 C.F.R. § 41.20(b)(2), or to credit any overpayment to Deposit Account No. **50-1627**.

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(1) REAL PARTY IN INTEREST

The real party in interest is Myriad Genetics, Inc., a corporation of the State of Delaware, having a place of business at 320 Wakara Way, Salt Lake City, Utah 84108, to whom all interest in the present Application has been assigned by virtue of an Assignment submitted on February 1, 2002, and recorded on February 20, 2002 (at reel 012639, and frame 0682).

(2) RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences that will directly affect, or be directly affected by, or have a bearing on, the Board of Patent Appeals and Interferences' decision in the present appeal.

(3) STATUS OF CLAIMS

Claims 1 through 68 are currently pending in the Application, although claims 24, 25, 27 and 60 have been canceled. Claims 28 through 43, and 51 through 59 are withdrawn from consideration. Claims 1-23, 26, 44-50, and 61-68 were finally rejected in a Final Office Action mailed on November 30, 2005, and are being appealed. Of these 39 appealed claims, Claims 1, 5, 8, 12, 17, 22, 23, 26, 44, 45, 50, 61, 63, and 64 are independent claims.

(4) STATUS OF AMENDMENTS

A final rejection was issued and mailed in this case on November 30, 2005. According to this final rejection, the Amendment dated August 24, 2005 and the Supplemental Amendment dated September 8, 2005 were entered into the record. A subsequent Amendment under 37 C.F.R. § 1.116 was filed on February 21, 2006 and an Advisory Action was mailed June 2, 2006, indicating that the Amendment under 37 C.F.R. § 1.116 was also entered into the record. The present appeal is based on the

listing of claims presented in the Amendment under 37 C.F.R. § 1.116, filed on February 21, 2006, which are reproduced in the attached Claims Appendix.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention relates to the inventors' discovery that the human tumor suppressor gene protein, Tsg101, interacts with the p6 portion of the human immunodeficiency virus type 1 (HIV1) GAG polyprotein (GAGp6), thus forming an intermolecular protein-protein complex between Tsg101 and HIV GAG. The interaction of these two proteins is required for HIV viral budding from host cells. Disruption of the interaction leads to the prevention of HIV budding and inhibition of HIV infection. Thus, the intermolecular protein-protein complexes can be used to screen for and identify compounds (drug candidates) that disrupt the interaction and are useful for treating HIV infection and AIDS. Importantly, the inventors further determined that the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 late domain are responsible for the interactions.

The rejected claims are drawn to (1) isolated protein complexes comprising Tsg101, fragments of Tsg101 comprising the UEV domain, or homologues thereof, interacting with HIV GAG, fragments of HIV GAG (such as GAGp6) comprising the late domain, or homologues thereof, (2) expression vectors encoding such interacting polypeptides, and (3) host cells containing such expression vectors. Importantly, the claims require that the fragments of Tsg101 and HIV GAG must retain the ability to interact. The relevant claims also require that the homologous proteins have a significant amino acid sequence identity to Tsg101 and HIV GAG and retain the ability to interact.

Independent claim 1 is representative of those claims directed towards isolated protein complexes comprising a first protein interacting with a second protein, wherein the first protein encompasses (a) full-length Tsg101, (b) a fragment thereof that comprises a UEV domain and interacts with an HIV GAGp6 late domain, (c) a first polypeptide that interacts with an HIV GAGp6 late domain and has an amino acid sequence that is at least about 75% identical to (a) or (b), and (d) a fusion protein comprising (a), (b), or (c); and the second protein encompasses (i) full-length HIV GAG,

(ii) a fragment thereof that comprises an HIV GAGp6 late domain and interacts with Tsg101, (iii) a second polypeptide that interacts with Tsg101 and has an amino acid sequence that is at least about 75% identical to that of (i) or (ii), and (iv) a fusion protein comprising (i), (ii), or (iii).

Independent Claim 44 is representative of the claims drawn towards expression vectors comprising a first nucleotide expression vector and a second nucleotide expression vector. In claim 44, the first nucleotide expression vector has a nucleic acid encoding a first protein which is selected from the group consisting of (i) full-length Tsg101, (ii) a fragment thereof that comprises a UEV domain and interacts with an HIV GAGp6 late domain, (iii) a first polypeptide having an amino acid sequence at least about 75% identical to that of (i) or (ii), and that interacts with an HIV GAGp6 late domain, and (iv) a first fusion protein comprising (i), (ii), or (iii). In claim 44, the second nucleotide expression vector has a nucleic acid encoding a second protein which is selected from the group consisting of (1) full-length HIV GAG, (2) full-length HIV GAGp6, (3) a fragment of (1) or (2) that interacts with Tsg101, (4) an HIV GAGp6 fragment that comprises an HIV GAGp6 late domain motif and interacts with Tsg101, (5) a second polypeptide that has an amino acid sequence at least about 75% identical to that of (1), (2), (3), or (4), and that interacts with Tsg101, and (6) a second fusion protein comprising (1), (2), (3), (4), or (5). Furthermore, Claim 44 requires that the first and second proteins must interact to form a protein complex.

Independent Claim 45 is representative of those claims directed to host cells comprising a composition substantially equivalent to the one recited in Claim 44.

Independent Claim 61 reads upon an expression vector comprising a first and second nucleic acid, wherein said first and second nucleic acids encode a first and second protein, respectively, wherein said encoded proteins are substantially identical to those recited in Claim 44, and wherein said first and second proteins interact to form a protein complex.

Independent Claim 63 is drawn to a non-human host cell expressing a first and a second protein substantially identical to those of Claim 1, wherein said first and second proteins must interact to form a protein complex within said non-human host cell.

Independent Claim 64 is substantially identical to Claim 63 except that, in this case, the host cell must be an isolated human host cell.

Support for the various elements of the independent claims can be found throughout the specification. However, the table below shows where specific passages of support can be found within the as-filed specification. Note that the passages cited are exemplary, and do not represent a comprehensive listing of where support for a particular element or aspect can be found.

Table 1. Location of support for claim elements within the as-filed specification

Element Or Aspect	Description / Identity / Characteristics	Location of Support in the Specification
1	Protein complexes comprising human Tsg101 interacting with HIV1 GAGp6	Table 1, p. 14; Example 1, pp. 79-80; and Example 3, pp. 81-83
2	Entrez nucleotide accession numbers encoding amino acid sequences of human Tsg101 and HIV1 GAGp6	Table 1, p. 14
3	Fragments of interacting proteins that retain the ability to interact	p. 38, ll. 5-6 & 27-29; p. 39, ll. 2-4 & 23-25; p. 40, ll. 23-27; and Example 4, pp. 83-84
4	Homologous proteins that retain the ability to interact	p. 11, l. 30 – p. 12, l. 13; and Example 3, pp. 81-83
5	Percent identity of homologous proteins	p. 12, l. 14 – p. 13, l. 4
6	Fusion proteins (general)	p. 11, ll. 21-29
7	Interactions & interaction domain (general)	p. 10, ll. 14-28
8	Protein complex & isolated protein complexes (general)	p. 10, l. 29 – p. 11, l. 20
9	Determining whether proteins interact	p. 10, ll. 14-23; and p. 61, l. 23 – p. 75, l. 17
10	In vitro screening/binding assays	p. 58 l. 18 – p. 61, l. 14; Example 4, pp. 83-84; and Figures 2, 3, and 4
11	In vivo screening/binding assays; esp. yeast two-hybrid assays	p. 61, l. 16 – p. 75, l. 17; Example 1, pp. 79-80, l. 12; and Example 3, pp. 81–83
12	Expression vectors	Section 4.3.1.1., p. 62-69
13	Reporters	Section 4.3.1.2., p. 70-72
14	Fusion proteins having DNA binding domains	p. 70, ll. 19-24; Example 1, pp. 79-80, l. 12; and Example 3, pp. 81–83
15	Fusion proteins having transcription-activating domains	p. 70, ll. 19-24; Example 1, pp. 79-80, l. 12; and Example 3, pp. 81–83

Element Or Aspect	Description / Identity / Characteristics	Location of Support in the Specification
16	Host cells for detecting protein-protein interactions	p. 45, ll. 6-9; p. 63, ll. 16-21; p. 64, ll. 14-19; p. 66, l. 27 – p. 67, l. 13; p. 69, l. 21 – p. 70, l. 13; Example 1, pp. 79-80, l. 12; and Example 3, pp. 81–83
17	The UEV domain of Tsg101	p. 33, ll. 26-27; p. 35, ll. 1-2 & 18-26; and p. 38, ll. 5-6 & 26-29
18	The late domain of HIV GAGp6 and viral budding	p. 33, l. 30 – p. 34, l. 10; p. 34, ll. 29-31; p. 36, l. 16 – p. 37, l. 16
19	The P(T/S)AP and P(T/S/I)(A/T)P motifs of viral GAG proteins	p. 34, ll. 11-31; p. 35, l. 18 – p. 37, l. 16; p. 39, l. 1 – p. 40, l. 27; and Example 3, pp. 81-83

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 1-23, 26, 44-50, and 61-68 are unpatentable under 35 USC § 112, first paragraph, as being based upon a disclosure with insufficient written description.
2. Whether Claims 1-23, 26, 44-50, and 61-68 are unpatentable under 35 USC § 112, first paragraph, as being based upon a nonenabling disclosure.

(7) ARGUMENT

In the finally rejected claims to isolated protein complexes, the two interacting proteins that are the elements of the claims, human Tsg101 and HIV GAG (or GAGp6), were well known in the art at the time of filing of the instant application. Appellant's specification clearly provides examples of fragments of these two proteins that interact and form protein complexes. Homologues of these two proteins were also known in the art. Further, Appellant's specification contains extensive disclosure on methods for identifying homologues and fragments and determining which of them retain the ability to interact with each other and form a protein complex. In view of the Federal Circuit's recent decisions in Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005), Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005), and Falko-Gunter Falkner, et al. v. Stephen C. Inglis, et al., No. 05-1324 (Fed. Cir. 2006), as well as the USPTO

Written Description Guideline Training Materials, the rejected claims clearly meet the written description and enablement requirements under 35 USC § 112, first paragraph. The Examiner's final rejections should be reversed. These rejections and Appellants' responses to these rejections are now presented.

A. Rejection under 35 USC § 112, first paragraph – written description

Claims 1-23, 26, 44-50, and 61-68 are finally rejected under 35 USC § 112, first paragraph as being based upon a disclosure that allegedly lacks sufficient written description of the invention.

In the Final Office Action, mailed November 30, 2005, the Examiner maintains that the claims (a) "are not limited the specific proteins or the binding regions that are known to interact;" (b) do not require that the binding domains be present or intact;" and the specification does not disclose "enough examples commensurate with the claims." These statements are not supported by the evidence in the record. Appellants respectfully traverse these rejections.

As a first matter, Appellants submit that in the present case, the Examiner has failed to provide a *prima facie* showing that sufficient written description is lacking because no evidence has been presented that one ordinarily skilled in the relevant art would reasonably believe that Appellant was not in possession of the invention at the time of filing. Instead, the Examiner's arguments comprise only allegations, which are not supported by any cited evidence.

The United States Patent and Trademark Office (PTO) has issued guidelines for the examination of patent applications under the 35 USC § 112, first paragraph, written description requirement. These guidelines state that the written description requirement of 35 USC § 112, first paragraph, can be met by:

> "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Guidelines for Examination of Patent Applications under 35 USC § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001) (emphasis added) (hereinafter "Written Description Guidelines"). This standard was adopted by the United States Court of Appeals for the Federal Circuit in Enzo Biochem Inc. v. Gen-Probe, Inc. 424 F.3d 1276 (Fed. Cir. 2005). In University of Rochester v. G.D. Searle, 358 F.3d 916 (Fed. Cir.2004), the Federal Circuit reaffirmed Enzo's use of the PTO written description guidelines, and recently, the Federal Circuit reaffirmed and applied the standard in Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005).

In Invitrogen, the patents-in-suit claimed a genetically modified reverse transcriptase (RT) in terms of two distinct functional attributes – namely DNA polymerase and RNase H activity. The disputed claims made use of these functional attributes to define a broad genus of modified RT polypeptides. Claim 1 of U.S. Patent No. 6,063,608 (the '608 patent) is representative. It reads:

> 1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

'608 patent, col. 19, lines 26-34 (claim 1) (emphasis added). As noted by the Federal Circuit, "[w]ith these patents Invitrogen thereby claims a compound (the polypeptide or genetically engineered RT) in terms of biological function (DNA polymerase and RNase H activity)." Id. at 1072 (emphasis added).

The '608 patent specification summarily provided only one single working example of an isolated RT polypeptide having DNA polymerase activity and substantially reduced RNase H activity as required in the claims at issue. See the '608 patent. Nevertheless, the Federal Circuit decisively affirmed the finding of the district court that the written description requirement was satisfied. Specifically, the Federal Circuit recognized that (1) the sequences of the RT gene family were known at the time of filing, and (2) the specification discloses methods of testing to determine that an enzyme comprising the disclosed amino acid sequence has the claimed functional features – DNA polymerase activity with substantially reduced RNase H activity.

Invitrogen, 429 F.3d at 1073-4. The court distinguished Invitrogen from University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) and Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993) in that the RT protein and gene sequences in Invitrogen were known in the art and that a single example of the claimed RT protein was provided in the specification. See Invitrogen, 429 F.3d at 1073-4.

The Federal Circuit's analysis in Invitrogen is directly applicable to the rejected claims at issue. Indeed, the facts in Invitrogen are directly analogous to the facts in the instant case. Appellant's claims are drawn to an isolated protein complex formed by the interaction between a native or modified human Tsg101 protein and a native or modified HIV GAG protein. See Claim 1. The Examiner apparently does not reject the aspect of protein complex formed by native human Tsg101 and HIV GAG proteins. What the Examiner rejected are the protein complexes comprising modified Tsg101 or modified HIV GAG proteins. Yet, with respect to the modified proteins at issue, they are directly analogous to the modified RT protein in the claims in Invitrogen, which were found to meet the written description requirement of 35 USC § 112, first paragraph.

Specifically, the modified Tsg101 protein in Claim 1 is defined by both a structural feature (amino acid sequence similarity/identity to native Tsg101 protein, or a native Tsg101 fragment) and a functional feature (the ability to interact with an HIV GAGp6 late domain). Likewise, the modified HIV GAG protein in Claim 1 is also defined by both a structural feature (amino acid sequence similarity/identity to native HIV GAG, or an HIV GAG fragment) and a functional feature (the ability to interact with native Tsg101).

Like the RT protein of Invitrogen, both human Tsg101 and HIV GAG were well known proteins in the art at the time of filing. Orthologs of such proteins from other species were also known. The nucleotide and amino acid sequences of both proteins and their orthologs were also known in the art by the filing date of this application.

As in the case of the '608 patent of Invitrogen, the instant specification discloses an example of protein fragments capable of forming the claimed protein complex. See Specification, page 14, Table 1. The specification also discloses the effect of specific mutations in the late domain PTAP motif on the interaction between full-length Tsg101 and the GAGp6 portion of the HIV1 GAG polyprotein. See Specification, Example 3,

pages 81-83, and Tables 3 and 4. The specification also discloses that fusion proteins consisting of a GST-tagged GAGp6 protein and a myc-tagged fragment of Tsg101 (comprising amino acid residues 1-207 of Tsg101) interacted in vitro. See Specification, Example 4, pages 83-84, and Figures 2, 3 and 4. This interaction was disrupted by a chemically-synthesized 14-amino acid oligopeptide that corresponded to the first 14 amino acid residues of HIV-1 GAGp6. See Id. Moreover, the specification provides extensive descriptions of various methods for making the modified Tsg101 and GAG proteins and preparing protein complexes, as well as various assays for determining whether such modified proteins meet the claimed functional feature, i.e., the ability to interact. See specification, page 11, line 30 through page 12, line 13; page 34, line 22 through page 35, line 2; page 36, line 16 through page 37, line 16; page 38, line 5 through page 41, line 4; page 41, line 25 through page 46, line 19; page 53, line 24 through page 56, line 2; page 61, line 24 through page 72, line 7; and Examples 1, 3 and 4, pages 79-80, 81-83 and 83-84, respectively.

Clearly, under Invitrogen, there is a sufficient written description in the specification for the modified proteins. Apparently, the rejected claims can be factually distinguished from Eli Lilly and Fiers because the Tsg101 and GAG proteins were known at the time of filing and Appellant's specification describes specific embodiments of the claimed invention. As such, Appellant's specification clearly meets the written description requirement under Invitrogen, while the findings of Eli Lilly and Fiers do not require a finding of lack of written description in the instant case.

Furthermore, the PTO's own Written Description Guidelines teach that a single species of polypeptide, disclosed through a combination of structural and functional attributes, is sufficient to describe a genus of related, variant polypeptides. See Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (2001). This is amply clear from the USPTO Revised Interim Written Description Guidelines Training Materials (hereinafter "USPTO Written Description Training Materials"). See USPTO Written Description Training Materials, http://www.uspto.gov/web/menu/written.pdf (last visited July 26, 2006).

In particular, Example 14 of the USPTO Written Description Training Materials deals with a hypothetical claim that reads: "A protein having SEQ ID NO:3 and variants

thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→ B." Example 14 further states that "[t]he specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. Id. at page 53. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein." Id. at page 53 (emphasis added). There is a single species specifically disclosed in the specification that is within the claim scope, that species being SEQ ID NO:3. Nevertheless, it is held in the USPTO Written Description Training Materials that the written description requirement is met in this case. As indicated, this is because the structures the species of the genus possess a specific degree of identity to SEQ ID NO:3, and the specification provides disclosure of an assay for identifying members possessing the claimed function, i.e., the catalytic activity.

The instant case is directly comparable to the scenario described in Example 14. In the instant case, the inventors have discovered that two known proteins – human Tsg101 and HIV GAG (esp., GAGp6) – specifically interact to form protein complexes. In Example 14, a single protein exhibits a specific catalytic activity. For the purposes of comparison, in the instant case the activities attributed to the pair of interacting proteins – namely, the ability of Tsg101 to specifically interact with GAGp6, and the ability of the GAGp6 to specifically interact with the Tsg101 – are analogous to the catalytic activity of the protein having SEQ ID NO:3 in the Example 14. In other words, in Example 14, the functional characteristic under consideration in the claim is catalysis (of the reaction of A→ B), whereas in the instant case, it is the ability to interact with a native protein (Tsg101 or GAGp6, accordingly). In both cases, the respective activities can be determined by assays disclosed in the respective specifications. In addition, while one single novel amino acid sequence of the protein in Example 14 of the Training Material is disclosed in the specification as SEQ ID NO:3, the Tsg101 and GAGp6 proteins in Appellant's case and their orthologs were well known in the art at the time of filing. Moreover, Appellants' specification discloses examples (by amino acid sequences) of interacting fragments recited in the claims. Further, various methods are well known in the art for making additional protein homologues and fragments and identifying those

capable of interacting. See specification, page 11, line 30 through page 12, line 13; page 34, line 22 through page 35, line 2; page 36, line 16 through page 37, line 16; page 38, line 5 through page 41, line 4; page 41, line 25 through page 46, line 19; page 53, line 24 through page 56, line 2; page 61, line 24 through page 72, line 7; and Examples 1, 3 and 4, pages 79-80, 81-83 and 83-84, respectively. Moreover, with respect to protein fragments, they are also defined by an additional structural feature, i.e., the interacting domain (GAGp6 late domain, or Tsg101 UEV domain). The structural feature of such domains are well known in the art. Clearly, following the USPTO Written Description Guidelines, the Examiner should have found a sufficient written description for Appellants' claims.

Thus, consistent with Federal Circuit precedent, and mirroring the claim specified in Example 14 of the USPTO Written Description Training Materials, the presently rejected claims meet the requirements of 35 U.S.C. § 112, first paragraph, as supported by adequate written description in the specification as filed. Therefore, Appellant respectfully requests that the written description rejection of claims 1-23, 26, 44-50, and 61-68, under 35 U.S.C. § 112, first paragraph, be reversed.

B. Rejection under 35 USC § 112, first paragraph – enablement

Claims 1-23, 26, 44-50, and 61-68 are finally rejected under 35 USC § 112, first paragraph for being based upon a disclosure that allegedly does not enable the full scope of the claimed invention.

In the Final Office Action, mailed November 30, 2005, the Examiner maintains the enablement rejection on the grounds that the specification "while being enabling for GAGp6 (449-500) and TSG101 (7-390), does not reasonably provide enablement for all other fragments, homologues, portions with less than 100% identity, and other GAGs or TSGs." The Examiner further alleges that the specification does not teach "what proteins/polypeptides are able to bind to form a complex as required by the claims;" and the examples provided are "not commensurate in scope with the claims." See Final Office Action, pages 4 and 5. Appellants respectfully disagree.

Enablement is a legal determination of whether a specification enables one skilled in the art to make and use the claimed invention without undue experimentation. Ratheon Co. v. Roper Corp., 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). In order to establish a prima facie case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). That is, the Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. Id.

The issue of enablement of biotechnological inventions under 35 USC § 112, first paragraph, was recently addressed by the Federal Circuit in Invitrogen Corporation v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005). In Invitrogen, the Federal Circuit considered whether the as-filed disclosure sufficiently enabled a claim drawn to a modified reverse transcriptase (RT) encoded by a modified RT gene and having DNA polymerase activity and substantially reduced RNase H activity, as recited above.

Specifically, as discussed above, claim 1 of the '608 patent is directed to a very broad genus of highly variant RTs. The claimed modified RT gene is derived from a collection of diverse organisms, ranging from viruses to primates. The claim does not recite, nor even mention, any sequence of nucleotides or amino acids, nor specific regions of the RT protein that are modified. Rather, the claimed RT is defined solely by functional limitations, specifically, as a modified reverse transcriptase having DNA polymerase activity and substantially reduced RNase H activity.

The patent specification in Invitrogen discloses two different M-MLV RT nucleotide sequences bearing deletion mutations, but only one was shown to encode an RT protein having the functional features of the claimed invention. Further, the specification provides no teachings on how to create a modified RT protein bearing a point mutation (as opposed to a deletion mutation) that would have the claimed functional features.

Yet, the Federal Circuit unequivocally held that the enablement requirement is satisfied for the full, broad, scope of the claim. Specifically, the court noted that "Invitrogen's teaching regarding deletion mutation is sufficient" "as it fully teaches a

mode of making the claimed invention," even though no teachings of point mutations were given and only one operative deletion mutation example was provided. Id. at 1070.

Here in Appellants' rejected claims, an isolated protein complex is defined as comprising two interacting polypeptides, which can be the native human Tsg101 and HIV GAG (or GAGp6) proteins, or a modified form thereof. The modified proteins are further defined by a structural feature (a minimal percent identity to the corresponding native protein), as well as the functional feature (interacting with either native HIV GAGp6 or human Tsg101, respectively). With respect to protein fragments, they are also defined by an additional structural feature, i.e., the interacting domain (GAGp6 late domain, or Tsg101 UEV domain).

Notably, as discussed above, the nucleotide sequences of the Tsg101 and GAG genes were known in the art at the time filing, as were the amino acid sequences of both proteins. The examiner asserts that Appellant's claims are not enabled as to the full scope of the protein homologues and fragments that interact to form protein complexes. This is clearly incorrect in view of Invitrogen. Specifically, orthologs of both human Tsg101 and HIV GAGp6, i.e. naturally occurring Tsg101 from non-human species, and HIV GAGp6 proteins from various related retroviruses and HIV isolates, were known in the art at the time of filing. Moreover, specific examples of protein fragments having the claimed features are disclosed in the specification. See specification, page 14, Table 1; and Examples 1, 3 and 4, pages 79-80, 81-83 and 83-84, respectively. In addition, an ordinarily skilled person in the art would know how to make modified human Tsg101 and HIV GAGp6 proteins having deletions, substitutions, insertions and/or additions by routine molecular biological (genetic engineering) techniques. Such modified proteins can be homologous to, or fragments of, the native proteins taught in the examples. For example, simple deletions of native proteins result in fragments of the full-length proteins, whereas substitutions result in homologous proteins. Regardless, the specification is replete with explanations of methods for making such homologues and fragments. See, e.g., specification, page 11, line 30 through page 12, line 13; page 34, line 22 through page 35, line 2; page 36, line 16 through page 37, line 16; page 38, line 5 through page 41, line 4; page 41, line 25 through page 46, line 19; page 53, line 24

through page 56, line 2; page 61, line 24 through page 72, line 7; and Examples 1, 3 and 4, pages 79-80, 81-83 and 83-84, respectively.

Furthermore, it is important to note that the rejected claims specify that any homologues used to create the protein complexes of the invention meet certain structural requirements, and have a minimal percent identity to the corresponding native protein (e.g., having at least 75% sequence identity with native human Tsg101 or HIV GAGp6). In addition, both the protein homologues and fragments must possess the capability to interact, a functional feature like that in the claims at issue in Invitrogen. Further, the specification teaches: "the UEV domain of the Tsg101 protein and the PTAP motif of the [late domain of] HIV GAGp6 are responsible for the interactions." See specification page 38, lines 5-6. Additionally the specification provides detailed descriptions of various assays for identifying those homologues and fragments satisfying the functional requirements of the claims. See Id. Clearly, one skilled in the art upon reading the specification would be enabled to make the homologues and fragments called for in the claims, and thus the claimed protein complex, without undue experimentation.

For example, one of ordinary skill in the art, upon reading the specification, would recognize that only a portion of Tsg101 is required to facilitate interaction with GAGp6, and visa versa. As noted above, the specification teaches that "the UEV domain of the Tsg101 protein and the PTAP motif of the [late domain of] HIV GAGp6 are responsible for the interactions." Additionally, Example 4 of the specification (pages 83-84) teaches the skilled artisan that a myc-tagged fusion protein comprising amino acid residues 1-207 of Tsg101 is capable of binding a GST tagged fusion protein comprising full-length GAGp6, and that this interaction can be disrupted by a synthetic oligopeptide corresponding to the first 14 amino acids of GAGp6. Further, the ordinarily skilled individual could, in fact, readily determine the minimal fragment of Tsg101 that retains the ability to interact with GAGp6, and visa versa, using routine experimentation, as taught by the specification. Once such minimal interacting fragments are identified, one of ordinary skill in the art would immediately appreciate that amino acid changes in the native proteins outside of the minimal peptide region would be unlikely to affect binding of Tsg101 to GAGp6.

Appellants further submit that, at the time of filing, it was a routine task for a skilled artisan to identify proteins homologous or orthologous to Tsg101 or HIV GAGp6, and to align such homologous or orthologous proteins and identify regions of conservation. As the skilled artisan would immediately appreciate, amino acid changes outside the identified regions of conservation (particularly the Tsg101 UEV domain and GAGp6 late domain) would be less likely to result in a loss of the of a modified protein to bind its native counterpart. Appellants further note that, at least in the case of Tsg101, such multi-sequence alignments were already known from the art, prior to the filing of the instant application. See, e.g., the alignment provided in Figure 1 of Koonin and Abagyan, *Nature Genetics* 16(4):330 (1997), submitted as Exhibit A in the Amendment of August 6, 2006.

Thus, one of ordinary skill in the art would know how to (1) perform alignments of amino acid sequences of homologous proteins, (2) identify conserved amino acid residues, (3) introduce conservative changes to specific residues in regions of proteins not exhibiting significant conservation, and (4) test whether the engineered variant proteins are still capable of interacting. Further, it can be reasonably predicted that protein homologues and fragments can be identified meeting the structural and functional limitations in Appellant's claims, and the examiner has presented no evidence to the contrary.

The Examiner has argued that undue experimentation would be required for an individual to make the fragments and homologues necessary to practice the full scope of the claimed invention. It is true that an extended time and effort might be required to identify all possible Tsg101 and GAGp6 fragments and homologues within the scope of the claims. However, "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in the art." Falko-Gunter Falkner, et al. v. Inglis, et al., (Fed. Cir. 2006, 05-01324) (quoting Board Op.) As the Federal Circuit further explained:

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance

with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

Johns Hopkins Univ. v. Cellpro., (Fed. Cir. 1998) (emphasis added).

In the instant case, the specification teaches that a Tsg101 fragment capable of interacting with HIV GAGp6 is, for example, "a fragment containing the UEV domain of the Tsg101 protein, specifically the amino acid residues 1-207, the amino acid residues 1-147, etc." Specification, page 38, lines 27-29. The specification also teaches that fragments of HIV GAG and "GAG polypeptides and fragments thereof from other retroviruses containing the P(T/S/I)(A/T)P late domain motif are believed to interact with Tsg101 in the same manner as the HIV GAG polypeptide. Thus they can be used in forming protein complexes with Tsg101 or a homologue or derivative or fragment thereof." Specification, page 39, lines 2-6.

In view of these teachings, and the relatively high level of skill in the art, Appellants respectfully submit that only routine experiments are required to make and identify all Tsg101 protein homologues and fragments capable of interacting with HIV GAGp6, and all HIV GAGp6 homologues and fragments capable of interacting with Tsg101. Further, the specific fragments disclosed in Table 1 and Examples 1 and 4 of the specification provide reasonable direction for such experiments. The extensive disclosure in the specification on the various methods of making and identifying the protein homologues and fragments meeting the claim limitations also provides significant guidance. With all of these identified teachings, other teachings embedded within the specification, and the teachings of the prior art regarding orthologous proteins, undue experimentation simply is not required on the part of a skilled artisan to practice the claimed invention, especially in view of the high level of skill in the art of molecular biology in engineering genes and proteins of specific sequence.

In view of the above arguments, Appellants contend that the rejected claims are fully enabled by the specification, and as such, meet the requirement of 35 U.S.C. § 112, first paragraph, enablement.

C. Conclusion

Appellants respectfully request that the rejection of claims 1-23, 26, 44-50, and 61-68 under 35 USC § 112, first paragraph – written description and enablement, be reversed.

The Director is hereby authorized to charge the required Appeal Brief filing fee of $250.00, for a small entity, as set forth in 37 C.F.R. § 41.20(b)(2), or to credit any overpayment to Deposit Account No. **50-1627**. A petition for a three-month extension of time is being filed concurrently with this response. Provisions for the payment of the necessary fee for this extension of time have been made in the petition. Therefore, it is believed that no other extension of time, nor any additional fees, are due with this brief. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency, or credit any overpayment, to Deposit Account no. **50-1627**.

Respectfully submitted for Appellants,

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(8) CLAIMS APPENDIX

Claim 1 (previously presented): An isolated protein complex having a first protein interacting with a second protein, said first protein being selected from the group consisting of:

(a) Tsg101,

(b) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(c) a first polypeptide that interacts with an HIV GAGp6 late domain and has an amino acid sequence that is at least about 75% identical to (a) or (b), and

(d) a first fusion protein comprising (a), (b), or (c);

and said second protein being selected from the group consisting of:

(i) HIV GAG,

(ii) a fragment of HIV GAG that comprises an HIV GAGp6 late domain and interacts with Tsg101,

(iii) a second polypeptide that interacts with Tsg101 and has an amino acid sequence that is at least about 75% identical to that of (i) or (ii), and

(iv) a second fusion protein comprising (i), (ii), or (iii).

Claim 2 (previously presented): The isolated protein complex of Claim 1, wherein said second protein is HIV GAGp6 or a fragment thereof that comprises an HIV GAGp6 late domain and interacts with Tsg101.

Claim 3 (previously presented): The isolated protein complex of Claim 1, wherein said first protein is said first fusion protein.

Claim 4 (previously presented): The isolated protein complex of Claim 1, wherein said second protein is said second fusion protein.

Claim 5 (previously presented): An isolated protein complex having:

a first protein which is a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain, or a first polypeptide that interacts with an HIV GAGp6 late domain and has an amino acid sequence that is at least about 75% identical to the Tsg101 UEV domain, interacting with

a second protein which is HIV GAGp6 or an HIV GAGp6 fragment that comprises an HIV GAGp6 late domain and interacts with Tsg101, or a second polypeptide that comprises an HIV GAGp6 late domain, interacts with Tsg101, and has an amino acid sequence that is at least about 75% identical to that of HIV GAGp6 or said HIV GAGp6 fragment.

Claim 6 (previously presented): The isolated protein complex of Claim 5, wherein said first protein is a fusion protein comprising said Tsg101 fragment or said first polypeptide.

Claim 7 (previously presented): The isolated protein complex of Claim 5, wherein said second protein is a fusion protein comprising (a) HIV GAGp6 or (b) said HIV GAGp6 fragment or (c) said second polypeptide.

Claim 8 (previously presented): An isolated protein complex comprising:

(a) a first protein which is selected from the group consisting of

(i) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(ii) a first polypeptide that interacts with an HIV GAGp6 late domain and has an amino acid sequence at least 90% identical to the Tsg101 UEV domain, and

(iii) a fusion protein comprising (i) or (ii); and

(b) a second protein selected from the group consisting of

(1) HIV GAG,

(2) an HIV GAG fragment that comprises an HIV GAGp6 late domain and interacts with Tsg101,

(3) an HIV GAG homologue that has an amino acid sequence at least about 90% identical to that of (1) or (2) and interacts with Tsg101,

(4) HIV GAGp6,

(5) an HIV GAGp6 homologue that has an amino acid sequence at least about 90% identical to that of HIV GAGp6 and interacts with Tsg101,

(6) an HIV GAGp6 fragment that comprises an HIV GAGp6 late domain and interacts with Tsg101, and

(7) a fusion protein comprising (1), (2), (3), (4), (5), or (6);

wherein said first and second proteins interact to form said isolated protein complex.

Claim 9 (previously presented): The isolated protein complex of Claim 8, wherein said HIV GAGp6 fragment comprises an amino acid sequence of SEQ ID NO:25 or SEQ ID NO:26.

Claim 10 (previously presented): The isolated protein complex of Claim 8, wherein said HIV GAGp6 fragment comprises an amino acid sequence of SEQ ID NO:31 or SEQ ID NO:32.

Claim 11 (previously presented): The isolated protein complex of Claim 8, wherein said HIV GAGp6 fragment has a contiguous span of at least 10 amino acid residues of a naturally occurring HIV GAGp6, said contiguous span comprising a P(T/S)AP late domain motif.

Claim 12 (previously presented): An isolated protein complex comprising:

a first protein which is a Tsg101 fragment comprising a UEV domain, or a first polypeptide that has an amino acid sequence at least 75% identical the Tsg101 UEV domain, wherein said Tsg101 fragment or said first polypeptide interact with an HIV GAGp6 late domain; and

a second protein which is a retrovirus GAG, a retrovirus GAG fragment comprising a P(T/S)AP late domain motif, or a homologue of said retrovirus GAG or said retrovirus GAG fragment that comprises a P(T/S)AP late domain motif and has an amino acid sequence that is at least about 75% identical to that of said retrovirus GAG or said retrovirus GAG fragment, wherein said retrovirus GAG, said retrovirus GAG fragment,

said homologue of said retrovirus GAG, or said homologue of said retrovirus GAG fragment interacts with Tsg101, and wherein said first and second proteins interact to form said isolated protein complex.

Claim 13 (original): The isolated protein complex of Claim 12, wherein said retrovirus is a lentivirus.

Claim 14 (original): The isolated protein complex of Claim 13, wherein said lentivirus is a primate lentivirus.

Claim 15 (original): The isolated protein complex of Claim 14, wherein said primate lentivirus is selected from the group consisting of HIV-1, HIV-2, HIV-3, and simian immunodeficiency viruses.

Claim 16 (original): The isolated protein complex of Claim 13, wherein said lentivirus is a non-primate lentivirus selected from the group consisting of bovine lentiviruses, feline lentiviruses, and ovine/caprine lentiviruses.

Claim 17 (previously presented): An isolated protein complex comprising:

(a) a first protein which is selected from the group consisting of

(i) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(ii) a first polypeptide that has an amino acid sequence at least about 90% identical to the UEV domain of Tsg101 and that interacts with an HIV GAGp6 late domain, and

(iii) a fusion protein comprising (i) or (ii); and

(b) a second protein which is selected from the group consisting of

(1) a retrovirus GAG comprising a P(T/S)AP late domain motif,

(2) a second polypeptide that has an amino acid sequence at least about 90% identical to that of said retrovirus GAG and that interacts with Tsg101,

(3) a fragment of (1) or (2) that comprises a P(T/S)AP late domain motif and interacts with Tsg101, and

(4) a fusion protein comprising (1), (2) or (3);

wherein said first and second proteins interact to form said isolated protein complex.

Claim 18 (original): The isolated protein complex of Claim 17, wherein said retrovirus is a lentivirus.

Claim 19 (original): The isolated protein complex of Claim 18, wherein said lentivirus is a primate lentivirus.

Claim 20 (original): The isolated protein complex of Claim 19, wherein said primate lentivirus is selected from the group consisting of HIV-1, HIV-2, HIV-3, and simian immunodeficiency viruses.

Claim 21 (previously presented): The isolated protein complex of Claim 18, wherein said lentivirus is a non-primate lentivirus selected from the group consisting of bovine lentiviruses, feline lentiviruses, and ovine/caprine lentiviruses.

Claim 22 (previously presented): An isolated protein complex comprising:

(a) a first protein which is selected from the group consisting of

(i) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(ii) a first polypeptide that interacts with an HIV GAGp6 late domain and has an amino acid sequence at least about 90% identical to that of the Tsg101 UEV domain, or said Tsg101 fragment, and

(iii) a fusion protein comprising (i) or (ii); and

(b) a second protein which is selected from the group consisting of

(1) a primate lentivirus GAG that interacts with Tsg101,

(2) a primate lentivirus GAG homologue that has an amino acid sequence at least about 90% identical to that of said primate lentivirus GAG and that interacts with Tsg101,

(3) a primate lentivirus GAGp6 that interacts with Tsg101,

(4) a primate lentivirus GAGp6 homologue that has an amino acid sequence at least about 90% identical to that of HIV GAGp6 and that interacts with Tsg101,

(5) a fragment of (1), (2), (3), or (4) that comprises a late domain motif and interacts with Tsg101, and

(6) a fusion protein comprising (1), (2), (3), (4), or (5);

wherein said first and second proteins interact to form said isolated protein complex.

Claim 23 (previously presented): An isolated protein complex comprising:

a first fusion protein comprising a Tsg101 fragment that interacts with an HIV GAGp6 late domain interacting with a second fusion protein comprising a fragment of HIV GAG comprising an HIV GAGp6 late domain motif.

Claim 24-25 (cancelled)

Claim 26 (previously presented): An isolated protein complex having a first polypeptide covalently linked to a second polypeptide, wherein said first polypeptide is a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain or a homologue of said Tsg101 fragment that has an amino acid sequence at least about 75% identical to said Tsg101 fragment, wherein said Tsg101 fragment or said homologue of said Tsg101 fragment interacts with an HIV GAGp6 late domain, and wherein said second polypeptide is HIV GAG or a fragment of HIV GAG that comprises an HIV GAGp6 late domain, a homologue of HIV GAG or said fragment of HIV GAG, that has an amino acid sequence at least about 75% identical to that of said HIV GAG or said fragment of HIV GAG, and said homologue interacts with Tsg101; and

wherein said first and second polypeptides interact to form said isolated protein complex.

Claim 27 (cancelled)

Claim 28 (withdrawn): A method for selecting modulators of a protein complex according to Claim 1, comprising:

providing the protein complex;

contacting said protein complex with a test compound; and

determining the presence or absence of binding of said test compound to said protein complex.

Claim 29 (withdrawn): A method for selecting modulators of an interaction between a first protein and a second protein,

(a) said first protein being selected from group consisting of

(i) Tsg101 protein,

(ii) a Tsg101 protein homologue having an amino acid sequence at least 90% identical to that of Tsg101 and capable of interacting with HIV GAGp6,

(iii) a Tsg101 protein fragment containing the Tsg101 UEV domain, and

(iv) a fusion protein containing said Tsg101 protein, said Tsg101 protein homologue or said Tsg101 protein fragment; and

(b) said second protein being selected from the group consisting of

(1) HIV GAG polypeptide,

(2) a HIV GAG polypeptide homologue having an amino acid sequence at least 90% identical to that of HIV GAG polypeptide and capable of interacting with Tsg101,

(3) HIV GAGp6 protein,

(4) a HIV GAGp6 homologue having an amino acid sequence at least 90% identical to that of HIV GAGp6 polypeptide and capable of interacting with Tsg101,

(5) a HIV GAGp6 fragment capable of interacting with Tsg101, and

(6) a fusion protein containing said HIV GAG polypeptide, said HIV GAG polypeptide homologue, said HIV GAGp6 protein, said HIV GAGp6 homologue or said HIV GAGp6 fragment, said method comprising:

contacting said first protein with said second protein in the presence of one or more test compounds; and

determining the interaction between said first protein and said second protein.

Claim 30 (withdrawn): The method of Claim 29, wherein at least one of said first and second proteins is a fusion protein having a detectable tag.

Claim 31 (withdrawn): The method of Claim 29, wherein said contacting step is conducted in a substantially cell free environment.

Claim 32 (withdrawn): The method of Claim 29, wherein said contacting step is conducted in a host cell.

Claim 33 (withdrawn): The method of Claim 32, wherein said host cell is a yeast cell.

Claim 34 (withdrawn): A method for selecting modulators of an interaction between a first protein and a second protein,

(a) said first protein being selected from group consisting of

(i) Tsg101 protein,

(ii) a Tsg101 protein homologue having an amino acid sequence at least 90% identical to that of Tsg101 and capable of interacting with HIV GAGp6,

(iii) a Tsg101 protein fragment containing the Tsg101 UEV domain, and

(iv) a fusion protein containing said Tsg101 protein, said Tsg101 protein homologue or said Tsg101 protein fragment; and

(b) said second protein being selected from the group consisting of

(1) a retrovirus GAG polypeptide having the P(T/S)AP late domain motif,

(2) a homologue of said retrovirus GAG polypeptide, said homologue having an amino acid sequence at least 90% identical to that of said retrovirus GAG polypeptide and capable of interacting with Tsg101,

(3) a fragment of said retrovirus GAG polypeptide, said fragment being capable of interacting with Tsg101, and

(4) a fusion protein containing said retrovirus GAG polypeptide, said retrovirus GAG polypeptide homologue or said retrovirus GAG polypeptide fragment, said method comprising:

contacting said first protein with said second protein in the presence of one or more test compounds; and

determining the interaction between said first protein and said second protein.

Claim 35 (withdrawn): The method of Claim 34, wherein said contacting step is conducted in a substantially cell free environment.

Claim 36 (withdrawn): The method of Claim 34, wherein said contacting step is conducted in a host cell.

Claim 37 (withdrawn): A method for selecting modulators of the protein complex of Claim 8, comprising:

contacting said protein complex with a test compound; and

determining the interaction between said first protein and said second protein.

Claim 38 (withdrawn): A method for selecting modulators of the protein complex of Claim 17, comprising:

contacting said protein complex with a test compound; and

determining the interaction between said first protein and said second protein.

Claim 39 (withdrawn): A method for selecting modulators of the protein complex of Claim 22, comprising:

contacting said protein complex with a test compound; and

determining the interaction between said first protein and said second protein.

Claim 40 (withdrawn): A method for selecting modulators of an interaction between a first polypeptide and a second polypeptide,

(a) said first polypeptide being selected from group consisting of

(i) Tsg101 protein,

(ii) a Tsg101 protein homologue having an amino acid sequence at least 90% identical to that of Tsg101 and capable of interacting with HIV GAGp6 late domain, and

(iii) a Tsg101 protein fragment containing the Tsg101 UEV domain; and

(b) said second polypeptide being selected from the group consisting of

(1) HIV GAG polypeptide,

(2) a HIV GAG polypeptide homologue having an amino acid sequence at least 90% identical to that of HIV GAG polypeptide and capable of interacting with Tsg101,

(3) HIV GAGp6 protein,

(4) a HIV GAGp6 homologue having an amino acid sequence at least 90% identical to that of HIV GAGp6 polypeptide and capable of interacting with Tsg101, and

(5) a HIV GAGp6 fragment capable of interacting with Tsg101, said method comprising:

providing in a host cell a first fusion protein having said first polypeptide, and a second fusion protein having said second polypeptide, wherein a DNA binding domain is fused to one of said first and second polypeptides while a transcription-activating domain is fused to the other of said first and second polypeptides;

providing in said host cell a reporter gene, wherein the transcription of the reporter gene is determined by the interaction between the first polypeptide and the second polypeptide;

allowing said first and second fusion proteins to interact with each other within said host cell in the presence of a test compound; and

determining the presence or absence of expression of said reporter gene.

Claim 41 (withdrawn): The method of Claim 40, wherein said host cell is a yeast cell.

Claim 42 (withdrawn): A method for selecting modulators of the protein complex of Claim 17, comprising:

providing in a host cell a first fusion protein containing said first protein, and a second fusion protein containing said second protein, wherein a DNA binding domain is fused to one of said first and second polypeptides while a transcription-activating domain is fused to the other of said first and second proteins;

providing in said host cell a reporter gene, wherein the transcription of the reporter gene is determined by the interaction between the first protein and the second protein;

allowing said first and second fusion proteins to interact with each other within said host cell in the presence of a test compound; and

determining the presence or absence of expression of said reporter gene.

Claim 43 (withdrawn): A method for selecting modulators of the protein complex of Claim 22, comprising:

providing in a host cell a first fusion protein containing said first protein, and a second fusion protein containing said second protein, wherein a DNA binding domain is fused to one of said first and second polypeptides while a transcription-activating domain is fused to the other of said first and second proteins;

providing in said host cell a reporter gene, wherein the transcription of the reporter gene is determined by the interaction between the first protein and the second protein;

allowing said first and second fusion proteins to interact with each other within said host cell in the presence of a test compound; and

determining the presence or absence of expression of said reporter gene.

Claim 44 (previously presented): A composition comprising:

(a) a first expression vector having a nucleic acid encoding a first protein which is selected from the group consisting of

(i) Tsg101,

(ii) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(iii) a first polypeptide having an amino acid sequence at least about 75% identical to that of (i) or (ii), and that interacts with an HIV GAGp6 late domain, and

(iv) a first fusion protein comprising (i), (ii), or (iii); and

(b) a second expression vector having a nucleic acid encoding a second protein selected from the group consisting of

(1) HIV GAG,

(2) HIV GAGp6,

(3) a fragment of (1) or (2) that interacts with Tsg101,

(4) an HIV GAGp6 fragment that comprises an HIV GAGp6 late domain motif and interacts with Tsg101,

(5) a second polypeptide that has an amino acid sequence at least about 75% identical to that of (1), (2), (3), or (4), and that interacts with Tsg101, and

(6) a second fusion protein comprising (1), (2), (3), (4), or (5);

wherein said first and second proteins interact to form a protein complex.

Claim 45 (previously presented): A host cell comprising:

(a) a first expression vector having a nucleic acid encoding a first protein which is selected from the group consisting of

(i) Tsg101,

(ii) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(iii) a first polypeptide that has an amino acid sequence at least about 75% identical to that of (i) or (ii), and interacts with an HIV GAGp6 late domain, and

(iv) a first fusion protein comprising (i), (ii), or (iii); and

(b) a second expression vector having a nucleic acid encoding a second protein selected from the group consisting of

(1) HIV GAG,

(2) HIV GAGp6,

(3) a fragment of (1) or (2) that comprises a late domain motif and interacts with Tsg101,

(4) a second polypeptide that has an amino acid sequence at least about 75% identical to that of (1), (2), or (3), and interacts with Tsg101, and

(5) a second fusion protein comprising (1), (2), (3), or (4);

wherein said first and second proteins interact to form a protein complex.

Claim 46 (original): The host cell of Claim 45, wherein said host cell is a yeast cell.

Claim 47 (previously presented): The host cell of Claim 45, wherein said first and second proteins are fusion proteins.

Claim 48 (previously presented): The host cell of Claim 45, wherein one of said first and second nucleic acids is operably linked to a nucleic acid encoding a DNA binding domain, and the other of said first and second nucleic acids is operably linked to a nucleic acid encoding a transcription-activation domain, whereby two fusion proteins can be produced in said host cell.

Claim 49 (original): The host cell of Claim 45, further comprising a reporter gene, wherein the expression of the reporter gene is determined by the interaction between the first protein and the second protein.

Claim 50 (previously presented): A host cell comprising:

(a) a first expression vector having a first nucleic acid encoding a first protein which is selected from the group consisting of

(i) Tsg101,

(ii) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(iii) a first polypeptide that has an amino acid sequence at least about 90% identical to (i) or (ii) and interacts with an HIV GAGp6 late domain, and

(iv) a first fusion protein comprising (i), (ii), or (iii); and

(b) a second expression vector having a second nucleic acid encoding a second protein selected from the group consisting of

(1) a retrovirus GAG that comprises a P(T/S)AP late domain motif and interacts with Tsg101,

(2) a retrovirus GAG fragment comprising a P(T/S)AP late domain motif that interacts with Tsg101,

(3) a second polypeptide that has an amino acid sequence at least about 90% identical to (1) or (2) and interacts with Tsg101, and

(4) a second fusion protein comprising (1), (2), or (3);

wherein said first and second proteins interact to form a protein complex.

Claim 51 (withdrawn): A method for providing a compound capable of interfering with an interaction between the first and second proteins in the protein complex of Claim 8 comprising:

providing atomic coordinates defining a three-dimensional structure of said protein complex; and

designing or selecting compounds capable of interfering with the interaction between said first protein and said second protein based on said atomic coordinates.

Claim 52 (withdrawn): A method for providing a compound capable of interfering with an interaction between the first and second proteins in the protein complex of Claim 17 comprising:

providing atomic coordinates defining a three-dimensional structure of said protein complex; and

designing or selecting compounds capable of interfering with the interaction between said first protein and said second protein based on said atomic coordinates.

Claim 53 (withdrawn): A method for providing a compound capable of interfering with an interaction between the first and second proteins in the protein complex of Claim 22 comprising:

providing atomic coordinates defining a three-dimensional structure of said protein complex; and

designing or selecting compounds capable of interfering with the interaction between said first protein and said second protein based on said atomic coordinates.

Claim 54 (withdrawn): A method for selecting a compound capable of inhibiting a protein-protein interaction between Tsg101 and HIV GAGp6, comprising:

contacting a test compound with a protein selected from group consisting of

(i) Tsg101 protein,

(ii) a Tsg101 protein homologue having an amino acid sequence at least 90% identical to that of Tsg101 and capable of interacting with HIV GAGp6,

(iii) a Tsg101 protein fragment containing the Tsg101 UEV domain, and

(iv) a fusion protein containing said Tsg101 protein, said Tsg101 protein homologue or said Tsg101 protein fragment; and

determining whether said test compound is capable of binding said protein.

Claim 55 (withdrawn): The method of Claim 54, further comprising testing a test compound capable of binding said protein for its ability to interfere with a protein-protein interaction between Tsg101 and HIV GAGp6.

Claim 56 (withdrawn): The method of Claim 55, further comprising testing a test compound capable of binding said protein for its ability to inhibit HIV viral budding from an HIV-infected host cell.

Claim 57 (withdrawn): A method for selecting a compound capable of inhibiting a protein-protein interaction between Tsg101 and HIV GAGp6, comprising:

providing atomic coordinates defining a three-dimensional structure of a protein selected from group consisting of

(i) Tsg101 protein,

(ii) a Tsg101 protein homologue having an amino acid sequence at least 90% identical to that of Tsg101 and capable of interacting with HIV GAGp6,

(iii) a Tsg101 protein fragment containing the Tsg101 UEV domain, and

(iv) a fusion protein containing said Tsg101 protein, said Tsg101 protein homologue or said Tsg101 protein fragment; and

designing or selecting compounds capable of interacting with said protein based on said atomic coordinates.

Claim 58 (withdrawn): The method of Claim 57, further comprising testing a compound capable of interacting with said protein for its ability to interfere with a protein-protein interaction between Tsg101 and HIV GAGp6.

Claim 59 (withdrawn): The method of Claim 57, further comprising testing a test compound capable of interacting with said protein for its ability to inhibit HIV viral budding from an HIV-infected host cell.

Claim 60 (cancelled)

Claim 61 (previously presented): An expression vector comprising:

(a) a first nucleic acid encoding a first protein which is selected from the group consisting of

(i) Tsg101,

(ii) a Tsg101 fragment that comprises a UEV domain interacts with an HIV GAGp6 late domain,

(iii) a first polypeptide that has an amino acid sequence at least about 75% identical to that of (i) or (ii) and interacts with an HIV GAGp6 late domain, and

(iv) a first fusion protein comprising (i), (ii), or (iii); and

(b) a second nucleic acid encoding a second protein selected from the group consisting of

(1) HIV GAG,

(2) HIV GAGp6,

(3) a fragment of (1) or (2) that comprises an HIV GAGp6 late domain motif and interacts with Tsg101,

(4) a second polypeptide that comprises an amino acid sequence at least about 75% identical to that of (1), (2), or (3) and that interacts with Tsg101, and

(5) a second fusion protein comprising (1), (2), (3), or (4);

wherein said first and second proteins interact to form a protein complex.

Claim 62 (previously presented): A host cell comprising the expression vector of Claim 61.

Claim 63 (previously presented): A non-human host cell expressing:

(a) a first protein which is selected from the group consisting of

(i) Tsg101,

(ii) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(iii) a first polypeptide that has an amino acid sequence at least about 75% identical to that of (i) or (ii) and interacts with an HIV GAGp6 late domain, and

(iv) a first fusion protein comprising (i), (ii), or (iii); and

(b) a second protein selected from the group consisting of

(1) HIV GAG,

(2) HIV GAGp6,

(3) a fragment of (1) or (2) that comprises an HIV GAGp6 late domain motif and interacts with Tsg101,

(4) a second polypeptide that has an amino acid sequence at least about 75% identical to that of (1), (2), or (3) and interacts with Tsg101, and

(5) a second fusion protein comprising (1), (2), (3), or (4);

wherein said first and second proteins interact to form a protein complex within said non-human host cell.

Claim 64 (previously presented): An isolated human host cell comprising:

(a) a first promoter operably linked to a first chimeric nucleic acid encoding a first protein selected from the group consisting of

(i) Tsg101,

(ii) a Tsg101 fragment that comprises a UEV domain and interacts with an HIV GAGp6 late domain,

(iii) a first polypeptide that has an amino acid sequence at least about 75% identical to that of (i) or (ii) and interacts with an HIV GAGp6 late domain, and

(iv) a first fusion protein comprising (i), (ii), or (iii); and

(b) a second promoter operably linked to a second chimeric nucleic acid encoding a second protein selected from the group consisting of

(1) HIV GAG,

(2) HIV GAGp6,

(3) a fragment of (1) or (2) that comprises an HIV GAGp6 late domain motif and interacts with Tsg101,

(4) a second polypeptide that has an amino acid sequence at least about 75% identical to that of (1), (2), or (3) and interacts with Tsg101, and

(5) a second fusion protein comprising (1), (2), (3), or (4);

wherein said first and second proteins interact to form a protein complex within said isolated human host cell.

Claim 65 (previously presented): The isolated protein complex of claim 5, wherein said first protein is said Tsg101 fragment which consists essentially of a UEV domain.

Claim 66 (previously presented): The isolated protein complex of claim 5, wherein said first protein is said Tsg101 fragment which comprises a portion of Tsg101 having no more than 207 contiguous amino acid residues, further comprising a UEV domain.

Claim 67 (previously presented): The isolated protein complex of claim 8, wherein said first protein is said Tsg101 fragment which consists essentially of a UEV domain.

Claim 68 (previously presented): The isolated protein complex of claim 8, wherein said first protein is said Tsg101 fragment which comprises a portion of Tsg101 having no more than 207 contiguous amino acid residues, further comprising a UEV domain.

(9) EVIDENCE APPENDIX

none

(10) RELATED PROCEEDINGS APPENDIX

none